REMARKS

Claims 1-5 are pending. Claims 1, 2, 4 and 5 have been amended.

Applicants respectfully submit that no new matter is introduced.

Interview Summary and 37 CFR 1.131 Declaration

Applicants thank Examiner Leslie Royds for the courtesy of a telephonic interview on March 9, 2011 with Applicants' representative, Wan Chieh Lee. The substance of the interview was a discussion of U.S. Patent No. 6,509,349 to Ogletree ("Ogletree") cited by the Examiner in the Office Action in view of the declarations submitted on October 16, 2007 and a substantially similar declaration submitted on October 22, 2007. The Examiner indicated that Ogletree describes a range of dosages that are within the scope of the pending claims and these ranges were not specifically addressed by the declarations. The Examiner indicated that a response to the outstanding office action would need to address the dosages described by Ogletree.

Rejection under 35 U.S.C. § 112

The Examiner has rejected claims 1-5 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner contends that phrase "a pharmaceutically acceptable excipients" as recited in claim 1 is allegedly indefinite, because "it is unclear if the instantly claimed invention may contain one pharmaceutically acceptable excipient or more than one pharmaceutically acceptable excipient." (Office Action, page 2). The Examiner also contends that the phrase "said pharmaceutically acceptable excipient" in claim 2 lacks antecedent basis because claim 1 does not recite the term in the singular form.

Solely to promote prosecution and without agreeing with this rejection, claim 1 has been amended to remove the phrase "a pharmaceutically acceptable excipients." Similarly, claim 2 is amended to recite a pharmaceutical composition "further comprising one or more pharmaceutically acceptable excipients, lubricants, binders, disintegrators, emulsifiers, stabilizers, corrigents and/or diluents." Support for this amendment can be found in the specification as originally filed, for example, pages 5 and 6 of the specification. In view of the Applicants' claim amendments, the Examiner's rejections under 35 U.S.C. § 112, second

paragraph is moot. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 1-3 under 35 U.S.C. § 102(e) as allegedly anticipated by Ogletree. In particular, the Examiner contends that Ogletree teaches a combination of (1) an ADP-receptor blocking anti-platelet drug; and (2) a thromboxane A_2 receptor antagonist; and (3) optionally aspirin, for the inhibition of platelet aggregation and thrombus formation, and that Ogletree describes "the ADP-receptor blocking anti-platelet drug that inhibits ADP-induced platelet aggregation may be…2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof…" (Office Action, page 3). The Examiner further contends that Ogletree discloses that "the aspirin may be employed in a daily dosage," and that compositions are prepared "with a physiologically acceptable vehicle, carrier, excipients, etc." (Office Action, pages 3-4).

Although the 37 CFR 1.131 Declarations by Dr. Fumitoshi Asai and the other co-inventors of the present application submitted on October 16, 2007 and October 22, 2007 were previously found by the USPTO, in a Notice of Allowance dated January 7, 2009, to be sufficient to remove Ogletree as prior art against the present application, the Examiner now contends that the declarations are allegedly insufficient to overcome, and antedate Ogletree. In particular, the Examiner contends in the Interview Summary mailed March 23, 2011 that "the declaration failed to show prior art conception and reduction of not only the combination of compounds recited in the claims, but also the particular ratio of compounds as recited in the instant claims…" The Examiner further contends that the ratio of the particular compounds "is disclosed by Ogletree." (Interview Summary of March 23, 2011).

As discussed further below, Applicants respectfully submit that the 37 CFR 1.131 Declarations by Dr. Fumitoshi Asai and the other co-inventors of the present application submitted on October 16, 2007 and October 22, 2007 are sufficient to overcome, and antedate, the Ogletree reference, as well as the previously pending claims and the claims as amended herein. Nonetheless, without acquiescing to the Examiner's rejection, and solely to expedite prosecution of the present application, claim 1 has been amended to remove the particular weight ratios of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin.

Applicants submit that the 1.131 Declarations submitted in October 2007 demonstrates prior conception and reduction to practice of pharmaceutical compositions comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine (referred to as "CS 747" or "747" in the Declaration) and aspirin. In addition, Applicants submit that the declarations also provide evidence of prior conception and reduction to practice of the weight ratios between 1:500 to 500:1.

As stated in MPEP 715.02, a 37 CFR 1.131 declaration "must establish possession of either the whole invention or something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it." *In re Tanczyn*, 347 F.2d 830, 146 USPQ 298 (CCPA 1965). As explained in MPEP 715.02, "a 37 CFR 1.131 affidavit is not insufficient merely because it does not show the identical disclosure of the reference(s) or the identical subject matter involved in the activity relied up." Moreover, Applicants may antedate a reference by "showing prior completion of one or more species which put him or her in possession of the claimed genus prior to the reference's or activity's date." MPEP 715.03.

The 1.131 Declarations submitted in October 2007 demonstrate that the inventors had conceived and reduced to practice combinations of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin prior to the §102(e) date of Ogletree. As can be seen from the declarations, pages 145, 146, 149, 152 and 154 provide evidence of prior conception and reduction to practice of combinations of CS 747 and aspirin at various weight ratios between 1:500 to 500:1. For example, pages 145 and 146 submitted with the declarations show specific combinations of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine (CS 747) and aspirin at ratios of 3:100, 6:100 and 1:10, where CS 747 was at a dose of 0.3 mg/kg, 0.6 mg/lg or 1 mg/kg and aspirin was at a dose of 10 mg/kg. As another example, pages 149, 152 and 154 show combinations of CS 747 and aspirin at ratios of 3:100 and 6:100. Applicants respectfully submit that these exemplary combinations shown in the declarations submitted in October 2007 provides evidence that the inventors were in possession of any combination of CS 747 and aspirin, including compositions having weight ratios between 1:500 to 500:1, prior to the §102(e) date of Ogletree.

The Declarations also describe using 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin, in weight ratios of between 1:500 to 500:1, as an effective treatment for inhibiting thrombus formation and reducing the

resultant thrombus weight in thrombus-induced rats. Pages 147-153 describe the conditions, experimental variables and results of a shunt thrombosis model in rats using a number of pharmaceutical formulations comprising various weight ratios of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin. Notably, a dramatic reduction in thrombus weight was observed for pharmaceutical compositions containing 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin with weight ratios of 3:100 and 6:100, which are between 1:500 to 500:1. Page 154 illustrates the results of the study, and demonstrate that combinations of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin are highly efficacious at inhibiting thrombus formation. Accordingly, the 1.131 Declarations provide ample evidence of pharmaceutical compositions comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin, as well the anti-thrombic effect of the pharmaceutical compositions. The various ratios of CS 747 and aspirin tested by Applicants provide clear evidence of Applicants' possession of species within their genus prior to Ogletree. Accordingly, Applicants submit that the Declaration clearly "establishes possession" of the full scope of the claimed invention prior to the §102(e) date of Ogletree.

As noted above, Applicants submit that Ogletree should be removed as a reference in view of the Applicants' earlier date of invention, as demonstrated in the Declarations submitted in October 2007. Nonetheless, without acquiescing to the Examiner's rejection of the declaration, and solely to expedite prosecution of the present application, Applicants will also traverse the Examiner's rejection based on the amended claims.

Ogletree does not disclose pharmaceutical compositions formulated with two active ingredients, said active ingredients consisting of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin. Instead, Ogletree describes combinations requiring both an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist for inhibiting platelet aggregation and thrombus formation (abstract). Although Ogletree states that "[a]spirin can be optionally present" (column 31, lines 32-27), these combinations relate to triple- or quadruple-active compound pharmaceutical formulations comprising (i) an ADP-receptor blocking antiplatelet drug, (ii) a thromboxane A_2 receptor antagonist, which also provide antiplatelet activities and, optionally, (iii) aspirin and/or (iv) a

cholesterol lowering agent. In other words, Ogletree describes certain pharmaceutical compositions comprising at least three or four pharmaceutically active agents, wherein aspirin is an optional agent in the formulation. Moreover, in the limited cases where aspirin may be present in the formulations of Ogletree, there must be at least three pharmaceutical agents: an ADP-receptor blocking antiplatelet drug, a thromboxane A_2 receptor antagonist, and aspirin, all three of which are active against platelet aggregation. In contrast, the amended claims are directed to compositions formulated with two active ingredients, said active ingredients consisting of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine, or a pharmaceutically acceptable salt thereof, and aspirin. Ogletree does not describe a pharmaceutical composition formulated with two active ingredients, said active ingredients consisting of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine, or a pharmaceutically acceptable salt thereof, and aspirin, as recited in the amended claims. Therefore, Applicants submit that Ogletree does not anticipate amended claim 1, or any of the claims depending therefrom. Accordingly, Applicants request withdrawal of the §102(e) rejections.

Rejection under 35 U.S.C. § 103

The Examiner also rejects claims 1-5 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ogletree in view of U.S. Patent No. 5,288,726 (Koike, *et al*). Applicants respectfully traverse this ground of rejections.

Applicants' amended claims are directed to pharmaceutical compositions formulated with two active ingredients, said active ingredients consisting of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine and aspirin. Ogletree does not teach or suggest that either the ADP-receptor blocking drug or thromboxane A_2 receptor antagonist, both required according to the disclosure of Ogletree, can be removed or replaced with other pharmaceutically active agents, such as aspirin, to achieve the same, or even similar results. Particularly, Ogletree states that "[t]he ADP-receptor blocking antiplatelet drug suitable for use herein includes antiplatelet drugs which inhibit ADP-induced platelet aggregation and include clopidogrel and/or ticlopidine and/or CS-747 (described herein), and **do not include drugs such as aspirin** which inhibit platelet aggregation by other mechanism" (col. 4, lines 25-30). Rather, an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist drug are

necessary components to the formulations described by Ogletree. Specifically, Ogletree states that "[i]t is believed that the combination of ADP-receptor blocking antiplatelet drug and thromboxane A_2 receptor antagonist…is a surprising and unique concept" and that "the combination may provide additional antiplatelet aggregation, anti-ischemic, anti-thrombus effects over which may be obtained using each of the components in the combination alone" (col. 4, l. 6-14). Accordingly, Ogletree teaches that both the ADP-receptor blocking antiplatelet drug and thromboxane A_2 receptor antagonist are critical to achieve the surprising effects, therby effectively *teaching away* from compositions that do not contain both an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist. Not only does Ogletree *teach away* from not using both an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist, excluding the thromboxane A_2 receptor antagonist would fundamentally change, and potentially destroy, the surprising results described therein. Accordingly, one of skill in the art, reading Ogletree would not exclude the thromboxane A_2 receptor from the pharmaceutical compositions described therein.

In sum, Ogletree, as a whole, relates to the combination of an ADP-receptor blocking antiplatelet drug and a thromboxane A_2 receptor antagonist. One of skill in the art, therefore, would not exclude the thromboxane A_2 receptor antagonist because the references teaches that it is critical for the antiplatelet aggregation, anti-ischemic and anti-thrombotic properties of the compositions. Moreover, one of skill in the art would not select the specific ADP-receptor blocking antiplatelet drug 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine, or a pharmaceutically acceptable salt thereof, and aspirin because the reference teaches away from such a combination.

As discussed above, Ogletree lacks the requirements of the claimed invention. Koike does not remedy the deficiencies of Ogletree. Koike describes various tetrahydrothieno[3,2-c]pyridine derivatives and their use for inhibiting blood platelet aggregation (col 1, l. 9-14), including 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydothieno[3,2-c]pyridine. Koike also describes that acid addition salts of these compounds, including hydrochloride and maleate salts, may be formed (col. 13, l.43-63), and that "compounds of formula (I) and their tautomers, salts and complexes of the present invention have an excellent inhibitory activity against blood platelet aggregation…" (col 39, l.30-38). Koike does not teach or suggest that the compounds described therein can be combined with other antiplatelet agents,

least of all aspirin. Accordingly, Ogletree and Koike, alone or in combination, fail to provide the elements of the claimed compositions.

In view of the above, Applicants respectfully request withdrawal of the §103 rejections.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this response to Deposit Account No. **50-3732**, Order No. 17620.105003. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 17620.105003.

Respectfully submitted,
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